Journal of Surgical Oncology 1999;71:155–161

Treatment and Local Control of Primary Extremity Soft Tissue Sarcomas

CONSTANTINE P. KARAKOUSIS, MD, PhD,[1]* AND DEBORAH L. DRISCOLL, BA[2]
[1]State University of New York at Buffalo, Kaleida Health, Millard Fillmore Gates-Hospital, Buffalo, New York
[2]Roswell Park Cancer Institute, Buffalo, New York

Background and Objectives: Modern series of adult extremity soft tissue sarcomas utilize combinations of modalities in all patients. Remaining questions: 1) is it necessary to strive for wide margins in the multimodality era; 2) to use adjuvant therapy in every high-grade sarcoma? 3) Does previous partial or marginal resection seriously interfere with the definitive resection?

Methods: In a retrospective review of 194 extremity soft tissue sarcomas (1977–1994), limb preservation was possible in 181/194 (93%) of cases. Patients with narrow margins received adjuvant radiation. Some patients were referred after partial (n = 39) or "complete" (n = 63) excision.

Results: Local recurrence was observed in 181/141 (13%) of patients treated with wide or compartmental resection, and in 10 of 42 (24%) of those treated with conservative resection plus radiation ($P = 0.14$). The 5-year survival rate for grade III, ≥5-cm sarcomas was not significantly different ($P = 0.82$) with adjuvant (46%) or without (48%) adjuvant systemic chemotherapy. Five-year survival varied ($P = 0.0001$) according to grade. Patients referred with partial, or "complete" (63%, 38/63, had residual tumor at reoperation) excision had a local recurrence rate of 8% and 6%, and 5-year survival rates of 75% and 84%, respectively.

Conclusions: 1) It is important to strive for wide margins even when adjuvant radiation is intended. 2) When a wide margin is possible, adjuvant radiation may not be necessary. 3) Adjuvant systemic chemotherapy may be considered for high-grade tumors, preferably within a prospective protocol. 4) A partial or "complete" excision of the tumor before referral to a tertiary center does not appear to compromise the limb preservation, local control, or survival rates of these patients.

J. Surg. Oncol. 1999:71:155–161.

KEY WORDS: adult extremity soft tissue sarcomas; local management

INTRODUCTION

There has been considerable improvement in the last 20 years in achieving limb preservation with adequate local control in extremity soft tissue sarcomas. In the past, at a time when surgical treatment was relied upon exclusively, the rate of amputation in cancer centers ranged from 40% [1] to 48% [2] for these tumors. At that time, the rate of local recurrence after wide resection was considerable, i.e., 28% [2] to 36% [1]; after local excision it was 65%[1], and after amputation 8% [1]. In one series, the rate of local recurrence after local excision was 90% [3].

More recently adjuvant radiation, preoperatively and/or postoperatively, has been used consistently in all of

The abstract of this manuscript was accepted for the 1998 International Cancer Conference of the UICC.

*Correspondence to: Constantine P. Karakousis, MD, PhD, Department of Surgery, Kaleida Health, Millard Fillmore Gates-Hospital, 3 Gates Circle, Buffalo, NY 14209. Fax No.: (716) 887-4220.
E-mail: ckarakou@mfhs.edu

Accepted 6 April 1999

TABLE I. Primary Extremity Soft Tissue Sarcomas (194 Total): Frequency of Histologic Subtypes

Histologic subtype	No.	Percent
Liposarcoma	58	30
Malignant fibrous histiocytoma	53	27
Leiomyosarcoma	21	11
Synovial sarcoma	16	8
Unclassified	9	5
Fibrosarcoma	9	5
Spindle cell sarcoma	6	3
Rhabdomyosarcoma	5	3
Hemangiosarcoma	5	3
Clear cell sarcoma	3	2
Epithelioid sarcoma	2	1
Malignant schwannoma	2	1
Other	5	3
Total	194	

the modern series. In some series, neoadjuvant radiation and intraarterial chemotherapy have been employed [4]. The implicit suggestion is that adjuvant therapy is obligatory for all, or at least for all high-grade (II and III) sarcomas, and that this is necessary in order to avoid the high local recurrence rates of the past or the need for frequent amputations. With the exception of one Swedish report advocating a selective approach in the use of local adjuvant therapy [5], there is no information whether a selective approach in using locally addressed adjuvant therapy may be a reasonable option which would be dependent on the expected or actual surgical margins.

Furthermore, there are no guidelines as to how the resection should be performed in the current era of consistent and universal use of combinations of modalities. The term "conservative" surgery is often employed. This may mean simply limb-preserving surgery, but it also can mean dissection not far from the palpable surface of the tumor. Local excision may often be the only limb-preserving surgical option in the distal portions of the extremities. Is local conservative resection justified in anatomical circumstances permitting a wide resection, just because one intends to use adjuvant radiation?

MATERIALS AND METHODS

This is a retrospective review of 194 patients with extremity soft tissue sarcomas treated at Roswell Park Cancer Institute, Buffalo, New York, during the period of 1977 to 1994. The mean follow-up time is 58 months, median 38 months. They were 97 men (50%) and 97 women (50%). Their mean age was 52, median 54 years. The histologic subtypes are listed in Table I. The grades of the tumors were grade I in 26 (13%), grade II in 53 (27%), and grade III in 115 (59%).

With regard to location, 24 were superficial to the investing fascia and 170 were deep tumors. Fifty-one tumors were located in the upper, and 143 in the lower extremity. Four of these tumors were located near a joint.

Of the total number of patients, 29 (15%) were referred with intact tumor, 63 (32%) with incisional biopsy, 39 (20%) with partial excision, and 63 (32%) with "complete" excision. Of the group of 63 patients with "complete" excision, 60 were reoperated for wider margins, while in 3 patients it was felt that the original surgery elsewhere was adequate.

The surgical treatment consisted of amputation in 13 patients (7%), compartmental resection in 61 (31%), wide excision in 112 (58%), and local excision in 8 (4%).

Patients with adequate surgical margins received no local adjuvant therapy. A gross, intracompartmental margin less than 2 cm was considered as inadequate. Due to the large size of most of the tumors, microscopic margins around the tumor circumference were not recorded in the pathology report for the majority of patients. For patients with compartmental resection, a less than 2-cm lateral margin was considered adequate as long as the dissection was carried out extracompartmentally and part of the margin consisted of a strong uninvolved fascia. In addition to the 8 patients with local excision, 32 of the 112 patients considered in the operative report to have had a "wide excision", had on pathologic examination an intracompartmental margin of <2cm at some point around the tumor circumference and were treated with radiation. Patients with large, high-grade sarcomas received adjuvant chemotherapy in a nonrandomized fashion, based on patient preference and/or recommendation by a Tumor Board. Thus, 112 (58%) patients were treated with surgery alone, 30 (15%) with surgery plus radiation, 29 (15%) with surgery plus systemic chemotherapy, 12 (6%) with surgery plus radiation plus systemic chemotherapy, 5 with surgery plus intraarterial chemotherapy, 4 with intraarterial chemotherapy plus radiation, and 2 with surgery plus a combination of systemic and intraarterial chemotherapy.

Radiation treatment, when given, was started about 3 weeks after the operation, except in the presence of a skin graft when a 5-week delay was allowed. The field covered the whole operative area initially, but after 4,500 cGy, was restricted to a smaller area corresponding to the site of narrow margin. A total tumor dose of 6,000 cGy over 6 weeks was delivered according to a fractionation schedule of 200 cGy/day, 1,000 cGy/week, using 4 or 6-MeV X-rays with source to skin distance of 100 cm or more, and a bolus along the surgical scar to neutralize the skin-sparing effect. Anteroposterior and posteroanterior parallel-opposed ports were used. Every effort was made to leave a strip of tissue in the medial or lateral aspect of the extremity out of the radiation field to preserve lymphatic drainage for the extremity.

Systemic chemotherapy consisted of the ADIC protocol (doxorubicin 50 mg/m^2 i.v. on day 1 and dacarbazine 200 mg/m^2 i.v. daily × 5) [6] repeated every 4 weeks for

six cycles. Intraarterial chemotherapy with the tourniquet infusion method employed doxorubicin 20 mg × 2 preoperatively, as described before [7].

Survival time was calculated from the date of resection to the date of last follow-up or death. Disease-free survival was calculated from the date of resection to the date of first recurrence or death, whichever occurred first. The method of Kaplan and Meier was used to estimate overall and disease-free survival distributions[8]. Tests of significance regarding survival distributions were based on the log-rank test [9]. Cox modelling was used for multivariate analysis [9]. *P* was regarded as significant at <0.05.

RESULTS

Local recurrence was noted in 15/112 (13%) of patients who were treated with surgery alone, in 6/30 (20%) of those treated with surgery plus radiation, in 3/29 (10%) of those treated with surgery plus systemic chemotherapy, and in 4/12 (33%) of those treated with surgery, radiation, and systemic chemotherapy ($P = 0.22$). No local recurrence was observed in five patients with preoperative intraarterial chemotherapy and surgery, or in four patients with preoperative intraarterial chemotherapy, resection, and postoperative radiation. One of two patients treated with intraarterial chemotherapy, resection, and systemic chemotherapy suffered local recurrence. Patients treated with surgery (± systemic chemotherapy) manifested local recurrence in 18/141 (13%) instances and those treated with surgery plus radiation (± systemic chemotherapy) did so in 10/42 (24%) ($P = 0.14$). Considering only the patients with grade II and III tumors, the local recurrence rate in the group of surgery (± systemic chemotherapy) was 17/119 (14%) and in the group of surgery and radiation (± systemic chemotherapy) it was 10/42 (24%) ($P = 0.14$). Two of the patients treated with adjuvant postoperative radiation developed radiation-induced sarcoma at the site of the previous resection and radiation 10 years after treatment. One of them with history of synovial sarcoma in the wrist developed multiple foci of spindle cell sarcoma in the area of radiation which then spread along the extremity. The other patient with a history of soft tissue sarcoma in the iliac fossa developed osteogenic sarcoma in the iliac bone of the same side. There was no significant difference ($P = 0.51$) in local recurrence according to the anatomic location of the soft tissue sarcoma (Table II). Specifically local recurrence was noted in 8/51 (16%) upper extremity sarcomas, and in 21/143 (15%) lower extremity sarcomas. Local recurrence was noted in 2/26 (8%) of patients with grade I tumors, 5/53 (9%) of those with grade II tumors, and in 22/115 (19%) of those with grade III tumors ($P = 0.14$).

There was a significant difference ($P = 0.006$) in local recurrence and survival rates according to referral status, owing probably to the fact that patients referred with "partial" or "complete" resection had smaller or favorable tumors, so that their wide, definitive resection was possible without difficulty (Table III). Of the 60 patients reoperated following "complete" excision elsewhere, 38 (63%) were found to have microscopic residual in the removed specimen.

TABLE II. Extremity Soft Tissue Sarcomas (194 Total): Anatomic Location and Local Recurrence (L.R.)

Location		No.	L.R. (%)
Upper extremity	Distal	18	4 (22)
	Proximal	30	4 (13)
Near a joint	3 in upper extremity	3	0
		51	
	1 in lower extremity	1	0
Lower extremity	Distal	37	3 (8)
	Proximal	105	18 (17)
		143	

The local recurrence rate in the period 1977 to 1982 for all patients treated was 10/42 (24%), in the period 1983 to 1987 it was 9/59 (15%), and in the period 1988 to 1994 it was 10/93 (11%), $P = 0.14$. In the first time period, 31% of the tumors were grade II and 55% grade III, in the second period 36% and 56%, and in the third period 20% and 63%, respectively ($P = 0.25$). In the first time period, 74% of the tumors were large (≥5 cm), in the second 85%, in the third 68% ($P = 0.07$). In the first time period 38% of the patients had adjuvant radiation, in the second 20%, in the third 19% ($P = 0.05$). In the first time period local recurrence was observed in 10/42 (24%), in the last two periods in 19/152 (12.5%) ($P = 0.09$).

Overall local recurrence was noted in 29/194 (15%). Of the 29 patients who suffered local recurrence, 6 (20%) required an amputation for its control.

Survival varied significantly according to the grade of the tumors (Fig. 1). The estimated 5-year survival rate was 90% for grade I, 84% for grade II, and 51% for grade III tumors ($P = 0.0001$). It also varied significantly according to tumor size. For tumors <5 cm ($n = 50$), the 5-year survival rate was 82% and for those ≥5 cm ($n = 144$), it was 60% ($P = 0.0009$). There was a trend toward variance in survival according to depth of location of the tumor. Thus, it was 88% at 5 years for the superficially located tumors ($n = 24$), and 63% for tumors located deep to the investing fascia ($n = 170$, $P = 0.10$). The estimated 5-year survival rate for the upper extremity tumors was 69%, and for the lower extremity tumors 64% ($P = 0.29$). The estimated 5-year survival rate for all patients was 62%.

Survival according to treatment is shown in Table IV. The surgery alone group had significantly better survival ($P = 0.02$) than the other treatment groups, apparently due to the favorable nature of the tumors selected for

TABLE III. Extremity Soft Tissue Sarcomas (194 Total): Referral Status, Local Recurrence, and Survival Rates

Tumor status	No.	Local recurrence (%)	5-year survival rate (%)
Intact	29	17	38
Incisional biopsy	63	27	52
Partial excision	39	8	75
"Complete" excision	63	6	84
		$P = 0.006$[a]	$P = 0.0004$[b]

[a]Based on Chi-squared analysis.
[b]Based on log-rank test, comparing Kaplan-Meier survival curves.

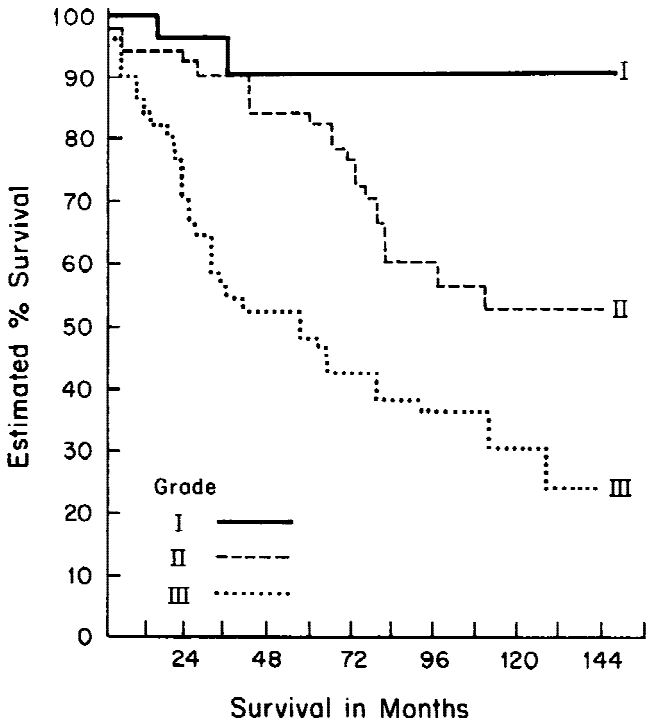

Fig. 1. Survival curves of patients with extremity sarcoma according to the tumor grade.

surgery alone. The 5-year survival rate for patients treated with surgery alone (n = 112) was 73%, while for all others (n = 82) treated with adjuvant radiation and/or chemotherapy, it was 56% ($P = 0.006$). Among patients with grade III tumors ≥5 cm in diameter, the 5-year survival rate for those with adjuvant chemotherapy (n = 36) was 46% and for those without adjuvant chemotherapy (n = 55) it was 48% ($P = 0.82$).

The 5-year survival rate for patients treated with local excision was 60%, wide resection 73%, compartmental resection 57%, and amputation 28% ($P = 0.32$).

DISCUSSION

In a recent report, it was concluded that routine use of adjuvant radiotherapy may not be necessary in all patients with adult soft tissue sarcomas [5]. The authors felt that wide resection alone may be performed in the majority of patients with primarily subcutaneous or intramuscular tumors, which comprise about two-thirds of soft tissue sarcomas of the extremities. By definition, subcutaneous tumors were those without invasion of the deep fascia, and intramuscular tumors were those that did not involve the surrounding muscle fascia and also did not have history of prior surgical treatment (open biopsy or resection) [5].

TABLE IV. Survival by Treatment

Treatment	No.	5-year survival (%)
Surgery only	112	73
Surgery and radiation	30	52
Surgery and chemotherapy	36	58
Surgery, radiation, and chemotherapy	16	61
		$P = 0.02$[a]

[a]Based on log-rank test, comparing Kaplan-Meier survival curves.

There have been two prospective randomized studies concerning the local treatment and control in extremity soft tissue sarcomas. In the first, local control and survival was compared between patients treated with amputation and those treated with limb-preserving resection and postoperative radiation [10]. Patients with limb preservation and radiation had a local recurrence rate of 15% [10]. In another report from the same center, the local recurrence rate in patients with conservative resection plus radiation was 9% [11].

In the second randomized study, patients were randomized between resection of the sarcoma alone and resection plus brachytherapy. In this report, patients undergoing a resection alone had a local recurrence rate of about 30% while those undergoing the combined treatment had a significantly lower rate of about 13% [12]. In the same report, in a nonrandomized group of 99 extremity sarcomas, 23% received brachytherapy; after 5 years of follow-up, the local recurrence rate in the brachytherapy group with presumably narrow surgical margins was about 35%, and in the surgery alone group it was about 30%—not significantly different [12].

In the past, local excision without further therapy resulted in high local recurrence rates in the range of 65% [1] to 90% [3]. Even with so-called wide resection, the rate of local recurrence was considerable, i.e., 28% [2] to 36% [1]. In most modern series employing combinations of modalities the rate has been in the range of 9% to 15% [10–14]. In one large study of 300 adult soft tissue sarcomas treated with conservative surgical excision and postoperative radiotherapy, the local recurrence rate was 22% [15]. In none of the modern series has there been an attempt to describe the surgical treatment in the multimodality context, or to correlate local recurrences with the extent of the surgical procedure. With marginal resection and brachytherapy the local recurrence rate is about 30% [16]. Although at the end of an operation

there may not be any evidence of macroscopic residual, positive microscopic margins are associated with a high rate of local recurrence despite the use of adjuvant modalities [17]. From the prospective randomized study discussed above [12], as well as from a comparison of the older and modern series, it appears that adjuvant radiation is capable of destroying residual microscopic disease in two-thirds of the patients having such residual. Modern series using adjuvant radiation in all patients have overall low local recurrence rates comparable to those of the present series, but since they represent a mixed population with surgical margins varying from a local excision to a wide resection, they do not allow an estimate of the expected local recurrence rate when a local resection is done and adjuvant radiation is given.

The present series, although not prospectively randomized, provides a direct comparison among concurrent patients—between those perceived to have had a wide resection without adjuvant radiation, and those with local excision given this adjuvant modality. Patients treated with resection alone (n = 112) without other local adjuvant modality had a local recurrence rate of 13%. The rate was similar (14%) in patients with grade II or III tumors who received no local adjuvant modality. These were patients with wide or compartmental resection in whom the surgical margins were considered to be adequate. There were no restrictions in this series related to anatomic location or prior open surgery in admitting or maintaining a patient in the surgery alone group, as previously suggested in another series [5], as long as a wide margin was expected and indeed achieved. Patients in whom local resection only was possible due to anatomical constraints during limb-preserving resection (n = 42), and who received adjuvant postoperative radiation as the sole local adjuvant therapy, had a local recurrence rate of 24%. At about 10 years' follow-up, two of the patients (4%) with adjuvant radiation developed a second radiation-induced sarcoma of a different histologic type in the irradiated area and died as a result. Radiation added to an operated area may also result in local fibrosis, lymphedema, and other complications from the treated extremity, particularly if the area of radiation involves a nodal basin [18]. Therefore, the above data suggest that wide or compartmental resection is legitimate as the sole local modality of treatment in a soft tissue extremity sarcoma when the local anatomy permits this type of resection, and may be preferable to a local excision plus radiation treatment. In our experience, such resection was possible in 76% of the patients, while conservative resection only was feasible in 24% of the patients and was supplemented with adjuvant radiation. Although there was a tendency for a decrease in local recurrence rates according to the extent of surgical treatment—25% for local excision, 16% for wide resection, 15% for compartmental resection, and 0% for amputation—the effect of the surgical treatment was affected by the application of adjuvant treatments for the more conservative resections, and the application of the more radical procedures usually for the larger tumors.

There is a widespread impression that prior biopsy, or worse, prior partial excision or local excision of a sarcoma, may unfavorably prejudice the applicability of limb-preserving surgery and local control. However, not 1 of 102 patients referred with partial or "complete" excision required an amputation due to inability to handle inappropriately placed incisions or to perform a satisfactory oncologic procedure. Although at times it may be difficult to encompass the previous incision and operative field in the center of the wide excision specimen, it should be nearly always possible to do so with some experience. Patients referred with partial or "complete" (63% of the latter were found to have microscopic residual at reoperation) resection had a significantly lower rate of local recurrence after the definitive procedure compared to patients referred with a tumor intact or only biopsied. The same phenomenon has been observed in the series from Sloan-Kettering Memorial Hospital and was interpreted as possibly meaning that two procedures instead of one should be done [19]. A more plausible interpretation is that patients referred with "complete" excision have, on the average, smaller tumors (hence a local excision or excisional biopsy is attempted at a community hospital often without the benefit of a prior biopsy); and that the surgeons in the referral center, not having the benefit of tumor palpability as a guide in their dissection, are forced to a really wide resection, where the result is a low rate of local recurrence. The contamination by partial resection of the incisional track remains confined in an extremity, and this entire area can be resected later en bloc with the underlying tumor. This would not be so in the case of a cavity (peritoneal or thoracic) where partial resection of a tumor is likely to result in widespread tumor spillage, dissemination, and an incurable situation.

Given the considerable local recurrence rates (about 30%) despite the addition of radiation therapy following marginal resection [16], it is clear that the availability of this fairly effective adjuvant modality should not be a cause for the surgeons to relax their vigilance toward the goal of obtaining the maximum margin allowed in each case by the considerations of limb preservation, adequate function, and proper wound healing. The surgical treatment remains the primary modality of treatment. In the thigh, for the large sarcomas, a compartment resection may be performed in the buttock, posterior, and medial compartments without appreciable sequelae on function concerning routine activities; while a modified anterior compartment resection, preserving extensor knee function, is applicable in most cases [20,21]. In the upper extremity or distal lower extremity, anatomical compart-

ment resection would result in unacceptable functional deficits, but a quasicompartmental resection is feasible. Thus, en bloc resection of the biopsy tract should be performed with an adequate margin at the level of the skin and subcutaneous fat. For a muscle involved by the tumor, it should be possible to obtain adequate margin in a longitudinal direction. Obviously, whether a small portion of or the entire involved muscle is removed, there is no difference in the potential functional deficit. The involved muscle(s) should be removed with a plane of dissection outside the fascia covering these muscles. Near a bone, major nerve, or vessel the periosteum or sheath respectively adjacent to the tumor mass is removed en bloc. For actual invasion by the tumor, major vessels may be resected en bloc and replaced with grafts [22] or a single motor nerve may be sacrificed [23], if this will satisfy the requirement for a grossly clean margin, in preference to an amputation. In summary, the oncologic surgeon operating on an extremity soft tissue sarcoma, even when it is preoperatively obvious that neoadjuvant or adjuvant therapy will be required, should attempt to procure a wide margin in all directions that this is anatomically and functionally feasible, although a lesser margin may be accepted in the vicinity of functionally critical structures which can be improved by resecting en bloc sheaths or fasciae (potential barriers to tumor spread) covering such structures. The aim of the oncologic surgeon always remains to minimize potential microscopic residual. Undue reliance to the adjuvant modalities should be avoided at the present stage of their development. Our data suggest a learning curve, since in the first 5-year period, our local recurrence rate was 24%, which then declined in the two successive periods to 15% and 11%, respectively, although the mix of the tumors concerning grade or size, or the use of adjuvant modalities did not change. They also suggest that for the larger tumors, early in the experience of a surgeon with the resection of these tumors, adjuvant radiation should be employed more frequently.

Gross tumor should not be left behind, because even with the use of adjuvant modalities, the local progression rate would be unacceptably high. Amputation is therefore required in patients in whom the location, size, and involvement of adjacent structures is such that an en bloc resection through grossly clean planes is not possible. In this series, including the surgical treatment of local recurrence, amputation was ultimately required in 10% of the patients.

In this retrospective study, adjuvant chemotherapy did not affect distant recurrence or survival rates as it is generally reported in the literature [24], and therefore the quest for an effective systemic modality for adult extremity soft tissue sarcomas remains open. It can be answered conclusively only through prospective randomized studies.

CONCLUSIONS

In summary, in cases of truly wide or compartmental resection of adult soft tissue extremity sarcoma, further adjuvant therapy may not be necessary for local control of the disease. Adjuvant radiation is an effective modality for local control at the primary site, which seems to work best in cases of minimal microscopic residual usually associated with wide excision. The local recurrence observed after local excision plus adjuvant radiation (24% in this series) suggests that local excision should be avoided even when adjuvant radiation is contemplated in anatomical areas of the extremities permitting a wide or compartmental resection. Prior partial or "complete" resection of a soft tissue sarcoma at a primary care center does not interfere substantially with limb preservation, local control, or survival of these patients. Ideally, however, these cases should be referred directly to tertiary centers to avoid the burden and morbidity for the patient of extra procedures.

REFERENCES

1. Abbas JS, Holyoke ED, Moore R, et al.: The surgical treatment and outcome of soft-tissue sarcoma. Arch Surg 1981;116:765–769.
2. Shiu MH, Castro EB, Hajdu SI, et al.: Surgical treatment of 297 soft tissue sarcomas of the lower extremity. Ann Surg 1975;182: 597–602.
3. Cadman NL, Soule EH, Kelly PJ: Synovial sarcoma. An analysis of 134 tumors. Cancer 1965;18:613–627.
4. Eilber FR, Eckardt JJ, Rosen G, et al.: Neoadjuvant chemotherapy with radiotherapy in the multidisciplinary management of soft tissue sarcomas of the extremity. Surg Oncol Clin North Am 1993;2:611–620.
5. Rydholm A, Gustafson P, Rööser B, et al.: Limb sparing surgery without radiotherapy based on anatomic location of soft tissue sarcoma. J Clin Onc 1991;9:1757–1765.
6. Pinedo HM, Kenis Y: Chemotherapy of advanced soft-tissue sarcoma in adults. Cancer Treat Rev 1977;4:67–86.
7. Karakousis CP, Kanter PM, Park HC, et al.: Tourniquet infusion vs. hyperthermic perfusion. Cancer 1982;49:850–858.
8. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–486.
9. Cox DR: Regression models and life-tables. J Royal Statistical Soc B 1972;187–220.
10. Rosenberg SA, Tepper J, Glatstein E, et al.: The treatment of soft-tissue sarcomas of the extremities: Prospective randomized evaluation of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305–315.
11. Potter DA, Kinsell T, Glatstein E, et al.: High-grade soft tissue sarcomas of the extremities. Cancer 1986;58:190–205.
12. Brennan MF, Casper ES, Harrison LB, et al.: The role of multimodality therapy in soft-tissue sarcoma. Ann Surg 1991;214:328–338.
13. Sim FH, Pritchard DJ, Reiman HM, et al.: Soft-tissue sarcoma: Mayo Clinic experience. Semin Surg Oncol 1988;4:38–44.
14. Suit HD, Mankin HJ, Wood WC, et al.: Preoperative, intraoperative, and postoperative radiation in the treatment of primary soft tissue sarcoma. Cancer 1985;55:2659–2667.
15. Lindberg RD, Martin RG, Romsdahl MM, et al.: Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer 1981;47:2391–2397.
16. Shiu MH, Hilaris BS, Harrison LB, et al.: Brachytherapy and

function-saving resection of soft tissue sarcoma arising in the limb. Int J Radiat Oncol Biol Phys 1991;21:1485–1492.
17. Rossi CR, Foletto M, Alessio S, et al.: Limb-sparing treatment for soft tissue sarcomas: The influence of prognostic factors. J Surg Oncol 1996;63:3–8.
18. Stinson SF, DeLaney TF, Greenberg J, et al.: Acute and long-term effects on limb function of combined modality limb sparing therapy for extremity soft tissue sarcoma. Int J Radiat Oncol Biol Phys 1991;21:1493–1499.
19. Lewis J, Leung D, Woodruff J, et al.: "Extremity soft tissue sarcoma: Are two operations better than one? Abstract Book, 49th Cancer Symposium." Atlanta, GA: Society of Surgical Oncology, 1996.
20. Karakousis CP: Modified anterior compartment resection. J Surg Oncol 1991;46:25–30.
21. Karakousis CP, Emrich LJ, Vesper DS: Soft-tissue sarcomas of the proximal lower extremity. Arch Surg 1989;124:1297–1300.
22. Karakousis CP, Karmpaliotis C, Driscoll DL: Major vessel resection during limb-preserving surgery for soft tissue sarcomas. World J Surg 1996;20:345–350.
23. Karakousis CP, Emrich LJ, Rao U, et al.: Feasibility of limb salvage and survival in soft tissue sarcomas. Cancer 1986;57:484–491.
24. Zalupski MM, Ryan JR, Hussein ME, et al.: Systemic adjuvant chemotherapy for soft tissue sarcomas of the extremities. Surg Oncol Clin North Am 1993;2:621–637.